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EXAMINER

GABEL, GAILENE

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/905,439

Applicant(s)

DOETSCH, VOLKER

Examiner

Gailene R. Gabel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 November 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44 is/are pending in the application.
- 4a) Of the above claim(s) 45-88 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-88 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group 1, claims 1-44, with traverse, filed 11/27/02 in Paper No. 9 is acknowledged and has been entered. Claims 45-88 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Currently, claims 1-88 are pending. Claims 1-44 are under examination.

Restriction Traversal

2. Applicant argues that the restriction requirement is based upon impermissible presumption that the point of patentability of restricted Group II is an exclusion of the ^{19}F nucleus from the set of available NMR-detectable nuclei.

In response, the restriction requirement was set forth for reason that Group 1 and Group 2 are each individually distinct and independent inventions, and not based upon a point of patentability for the exclusion of the ^{19}F nucleus. The record set forth in the previous restriction requirement clearly indicated that the delineated inventions are in fact patentably distinct each from the other or independent from the other.

3. Applicant argues that the restriction requirement is based upon a position that a method combination comprising use of any NMR-detectable nucleus can lack a utility

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allegedly possessed by the suggested subcombination comprising use of any NMR-detectable nucleus but one.

In response, the restriction requirement was not based on lack of utility of one method over the other; but rather, on the premise that Group 1 and Group 2 are each individually distinct and independent inventions which have been determined to relate as combination and subcombination. Inventions in this relationship are distinct by showing that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has separate utility, i.e. by itself or with other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the subcombination requires that the NMR-detectable nucleus is not ^{19}F . The subcombination has separate utility such as for use in screening drug or stimulus modulation or inhibition of intracellular proteins.

4. Applicant argues that examination of all 88 claims in the application will not pose serious undue burden to Examiner. Applicant argues that to establish undue burden, Examiner must show that the examination of the claims would involve substantially different prior art searches making co-examination burdensome, by showing separate classification, and by acquiring a separate status in the art.

In response, Examiner has established undue burden by exemplifying and establishing separate classifications as set forth in the previous Office Action and acquiring a separate status in the art from distinct structural requirements for each

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independent method. Each search status further bifurcates to separate fields of search, possibly overlapping and not necessarily coextensive, lines of search and strategy, etc. Thereinafter, extensive evaluation of the prior art searched and their relevancy in comparison to each particular limitation in every claim to evaluate extent of novelty and obviousness between each distinct invention differ as well. Therefore, Applicant's contention that there is no serious burden imposed upon an Examiner by rejoining all claims in the application is without merit.

Accordingly, the requirement is still deemed proper and is therefore made FINAL for reasons of record.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. Correction is required.

The oath or declaration is defective because:

- 1) It does not state that the person making the oath or declaration believes the named inventor to be the original, first, and sole inventor of the subject matter which is claimed and for which a patent is sought.
- 2) It does not identify the mailing or post office address of the inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

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- 3) It does not identify the city and either state or foreign country of residence of the inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, preamble is vague and indefinite in reciting, "in an amount greater than is naturally abundant" because the term "greater" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 1 is indefinite in reciting, "NMR". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims. See also claims 3, 15, 16, and 17.

Claim 1, step c) is vague and indefinite in reciting, "analyzing said data set to extract said structural information" because it implies but fails to positively recite, "extracting said structural information from the NMR data set for the selected macromolecule" as required by the preamble.

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Claim 5 is vague and indefinite in reciting, "small" in reference to the size of a molecule. The term "small" is a relative term that lacks a comparative basis for defining its metes and bounds. See also claims 6, 7, 8, 12, 13, and 19.

Claim 13 is vague and indefinite in reciting, "combinations thereof" because it is unclear what complex formation results from the recitation of "combinations thereof".

Claim 16 is indefinite in reciting, "HSQC and TROSY". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 19 lacks antecedent support in reciting, "NMR sensitive nucleus".

Claim 26 is non-idiomatic and, therefore, confusing in reciting, "experiences".

Claim 26 is vague and indefinite because it is unclear how the viscosity of the macromolecule relates to the structural information, etc. of the macromolecule recited in claim 1 from which it depends.

Claim 36 is indefinite in reciting, "HNCA". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 37 is indefinite in reciting, "HMQC". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

7. Claims 1-5, 10, 11, 13, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, and 41-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (¹⁹F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)).

Williams et al. teach extracting structural or conformational information from NMR data set for macromolecules, i.e. overexpressed proteins (glycolytic enzymes: hexokinase (HXK, 104 kDa), phosphoglycerate kinase (PGK, 45 kDa), and pyruvate kinase (PYK)) in an intact biological compartment, i.e. intact cell (yeast *Saccharomyces cerevisiae*), using ¹⁹F NMR (NMR detectable nucleus) longitudinal relaxation time measurements to assess their rotational mobility in the intact cells. The enzymes in the cells are labeled by biosynthetic incorporation of 5-fluorotryptophan. Williams et al. specifically determine the extent of enzyme immobilization as the result of complexation (tight binding) to other cellular macromolecules by comparing their visibility of the ¹⁹F resonances in spectra of intact cells with that of disrupted cell preparations (see Abstract, page 490, column 2, and 497, column 1). The yeast cells were prepared by transformation with one of three plasmids by operably linking (insertion) the coding sequence for the yeast enzymes into LEU-2-expressing plasmid (pKV49) where they

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were under the control of a PGK promoter. This non-native promoter is constructed by replacing the PGK UAS with the GAL-4 dependent GAL1-10 UAS. Expression from this vector is allowed in the presence of galactose and absence of glucose; thus, can be regulated or inhibited by manipulation of the growth medium. Restriction fragments containing the coding sequence for the enzymes were inserted into the expression site of pKV49. Some cells were transformed using URA-3-containing plasmid, pUG41S. The transformed cells were incubated (grown) in a medium, induced, labeled, then set in a buffer suspension (see page 490, column 2 to page 491, column 1: Yeast transformation and enzyme induction and Cell immobilization and perfusion). For ^{19}F NMR measurement of the conformation (rotational mobility) of the proteins in vivo, Williams et al. teach contacting the cells with radio frequency using UnityPlus 400 MHz spectrometer to excite the ^{19}F NMR, wherein the resonant frequency of ^{19}F at this field is 376.29 MHz. Williams et al. teach collecting radio frequency data; thereby producing NMR data set so as to analyze structural information of the enzymes from the data set. Viscosity of the enzymes were also measured to be 2-fold greater than viscosity of pure water (see page 491, column 2, Figures 1 and 2, and page 496, column 1). Williams et al. suggest application of these measurement studies in measuring translational diffusion coefficients of HXK and PGK in the cell using pulse field gradient techniques, which have been used with hemoglobin in human cell, i.e. erythrocytes.

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8. Claims 1-4, 10, 11, 15-17, 21, 29, 32, and 38-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Serber et al. (High-Resolution Macromolecular NMR Spectroscopy Inside Living Cells, J. Am. Chem. Soc., 123: 2446-2447 (February 2001)).

Serber et al. teach using high-resolution In-cell NMR spectroscopy to provide conformational information, i.e. three dimensional structures, in the form of NMR spectra, of macromolecules such as overexpressed proteins, i.e. MerA, inside living bacterial cells (E. coli) (see page 2446, column 1). MerA, which is labeled with ^{15}N (NMR detectable nucleus), is first grown in unlabeled LB medium, then protein production is induced following transfer of bacteria into ^{15}N labeled minimal medium. After harvest, the cells are contacted with radio frequency to excite the ^{15}N label; thereafter, [^{15}N , ^1H]-HSQC spectral data is collected, and then analyzed using 500 MHz NMR spectrometer equipped with a 5 mm triple resonance cryoprobe (see page 2446, column 2 and Figure 1). Serber et al. suggest application of the method in eukaryotic yeast cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (¹⁹F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)).

Williams et al. have been discussed supra. Williams et al. also discuss steady increase in concentration of the protein enzymes over 24 hours after induction (see page 492, column 2). In Table 1, Williams et al. comparatively tabulates cellular enzyme activities, concentrations, and induction levels.

Williams et al. differ from the instant invention in failing to teach concentration levels of the macromolecules, i.e. proteins, in the biological compartments, i.e. cells; in claim 27, 0.3% compared to the total weight of the cell and in claim 28, up to 50% compared to the total weight of the cell.

It is, however, maintained that induction of protein expression so as to reach specific levels of concentration in comparison to the total weight of the cell within which it resides, are all result effective variables which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant

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has not disclosed that the specific limitations recited in instant claims 27 and 28 are for any particular purpose or solve any stated problem and Williams et al. teach that in NMR spectroscopic art, protein expression induced to specific levels in comparison to the total weight of the cell, often vary according to the sample being analyzed or label being used, and various other parameters appear to work equally as well; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the methods disclosed by the prior art by normal optimization procedures.

10. Claims 6-9, 12, 19, 20, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (¹⁹F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Brown (US 817,474) and in further view of Fesik et al. (US 5,989,827).

Williams et al. has been discussed supra. Williams et al. differ from the claimed invention in failing to teach that the macromolecule is further labeled with deuterium. Williams et al. further differ from the instant invention in failing to teach that during cell preparation, the cell is incubated in deuterated medium that comprises an amino acid labeled with NMR sensitive nucleus.

Brown discloses a method for determining three-dimensional structural conformation of a protein by growing a mammalian cell culture which produces the protein in a nutrient medium which contains all amino acids that are essential for the growth of cells, and wherein the amino acids are substantially isotopically labeled with

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NMR active isotope. Brown further discloses a method for determining three-dimensional structural conformation of a first molecule that is complexed with a second molecule wherein at least one of the molecules is a protein. In this scenario, the first molecule is labeled with a stable NMR-active isotope and the second molecule is labeled with a deuterium, then the complex is subjected to NMR spectroscopic analysis.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to label the macromolecules or large proteins in the method of Williams with deuterium or heavy hydrogen as taught by Brown because Brown specifically taught that in substantially larger proteins wherein many of the resonances from individual atoms become too broad, it is reported that triple labeling, i.e. partial incorporation of deuterium ^2H as well as ^{13}C and ^{15}N isotopes, narrowed significantly the otherwise broadened lines in a larger molecule (see Brown, column 2, lines 55-67). Further, one of ordinary skill in the art at the time of the instant invention would have been motivated to label the protein in the method of Williams with deuterium as taught by Brown because Brown specifically taught that in materials containing hydrogen, i.e. water as contaminant to soluble materials or proteins, interfering effect of hydrogen can be rendered "invisible" in the hydrogen NMR spectrum by replacing all of ^1H with ^2H (deuterium).

Williams et al. and Brown differ from the instant invention in failing to disclose that the second molecule complexed with the first molecule, which is a protein, is a small exogenous molecule wherein the small molecule is a candidate therapeutic agent. Williams et al. and Brown further differ from the instant invention in failing to disclose

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using multidimensional multinuclear methods such as HNCA experiment and HMQC experiment.

Fesik et al. disclose identifying a small molecule ligand to the protein (target biomolecule) using two-dimensional $^{15}\text{N}/^1\text{H}$ NMR correlation spectroscopy, then identifying a second small molecule ligand to the protein using two-dimensional $^{15}\text{N}/^1\text{H}$ NMR correlation spectroscopy. Thereafter, Fesik et al. disclose forming a ternary complex by binding the first and second small molecules to the protein and determining the three-dimensional structure of the ternary complex and thus, the spatial orientation of the first and second small molecules on the protein. The small molecules are linked together to form a candidate therapeutic drug (see columns 2 and 3). The three dimensional structure of a ternary complex is determined using multidimensional multinuclear methods HNCA spectrum and HMQC spectrum.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the second molecule complexed with the protein in the method of Williams as modified by Brown with a candidate therapeutic drug as in the method of Fesik wherein the binding is analyzed using three-dimensional multinuclear analysis by HNCA or HMQC because Brown specifically taught application of his method to complexation of the protein with another molecule, and Fesik specifically taught that his method allows for identification, not only of the ability of candidate therapeutic compounds to bind the target protein, but also to form a physical association with the target protein to provide an ability to alter the function, i.e. intracellular or physiological, of the target protein and measure its effect using NMR spectroscopy.

11. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Adams et al. (US 5,378,620).

Williams et al. has been discussed supra. Williams et al. differ from the instant invention in failing to disclose administering a sufficient amount of inhibitor such as rifampicin, to the cell to cause inhibition of transcription in the cell.

Adams et al. disclose rifampicin as an antibiotic that inhibits RNA polymerase in bacteria, i.e. E. coli, that exhibits LEU-2-expressing plasmid. NMR Spectroscopy, using ^{15}N , ^1H , ^{13}C , ^{13}P and ^2H is used in studying bacterial protein structure in solution as effected by rifampicin inhibition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer an inhibitor such as rifampicin such as taught by Craig, to a bacterial cell for example, to inhibit transcription in the cell, or to a yeast cell transformation by operably linking the coding sequence for the yeast enzymes into LEU-2-expressing plasmid as taught by Williams because rifampicin as taught by Craig provides selective inhibition effects to transcription in cells that are under the control of specific promoters, while otherwise allowing study of structural information in desired protein structures, i.e. overexpressed proteins, using NMR Spectroscopy.

Remarks

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12. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Pervushin et al. (US 6,133,736) disclose a method of obtaining a nuclear magnetic resonance NMR correlation spectrum of heteronuclear spin systems, in particular comprising large molecules, especially biological macromolecules in solution (see Abstract).

Yamazaki et al., (J. Am. Chem. Soc. 120: 5591-5592 (May 1998)) teach segmental isotope labeling for protein NMR using peptide splicing.

Kay et al. (Three-Dimensional Triple-Resonance NMR Spectroscopy of Isotopically Enriched Proteins, Journal of Magnetic Resonance, 89: 496-514 (1990)) teach applications of HNCA and HMQC on isotopically enriched proteins.

Gronenborn et al. (Rapid Screening for structural integrity of expressed proteins by heteronuclear NMR spectroscopy, Protein Science 5: 174-177 (1996)) teach assessing the structural integrity of overexpressed proteins in crude E. coli extracts.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the

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organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
February 14, 2003



CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800-1641

2/24/03